Centro Servizi Università Policlinico di Modena

Modena, 23 novembre 2018

I NUMERI DEL CANCRO IN EMILIA ROMAGNA:
AMBIENTE, STILI DI VITA, SCREENING
FOCUS SU TUMORI DEL POLMONE E COLON-RETTO

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
Istituto di Ricovero e Cura a Carattere Scientifico

Immunoterapia: evoluzione e selezione del paziente

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Summary of PD-1/PD-L1 Immune Checkpoint Inhibitors Approved for Advanced NSCLC

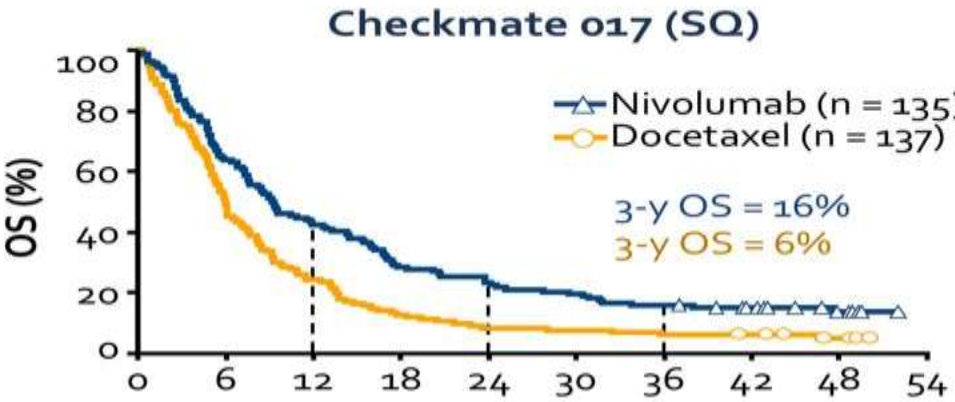
	Nivolumab[1] (Anti–PD-1)	Pembrolizumab[2] (Anti–PD-1)	Atezolizumab[3] (Anti–PD-L1)
Dose/schedule	240 mg every 2 wks; 480 mg every 4 wks	200 mg every 3 wks	1200 mg every 3 wks
Requirement for PD-L1 expression/approved settings	No; second line or later	▪ First-line monotherapy if ≥ 50% PD-L1 expression ▪ First line in combination with chemotherapy* ▪ After chemotherapy if ≥ 1% PD-L1 expression	No; second line or later
PD-L1 IHC assay	Dako 28-8[4]	Dako 22C3[5]	Ventana SP142[6]
Definition of PD-L1 positive	PD-L1(+): ≥ 1% Strong(+): ≥ 5%	PD-L1(+): ≥ 1% Strong(+): ≥ 50%	PD-L1(+): ≥ 50% TC or ≥ 10% IC

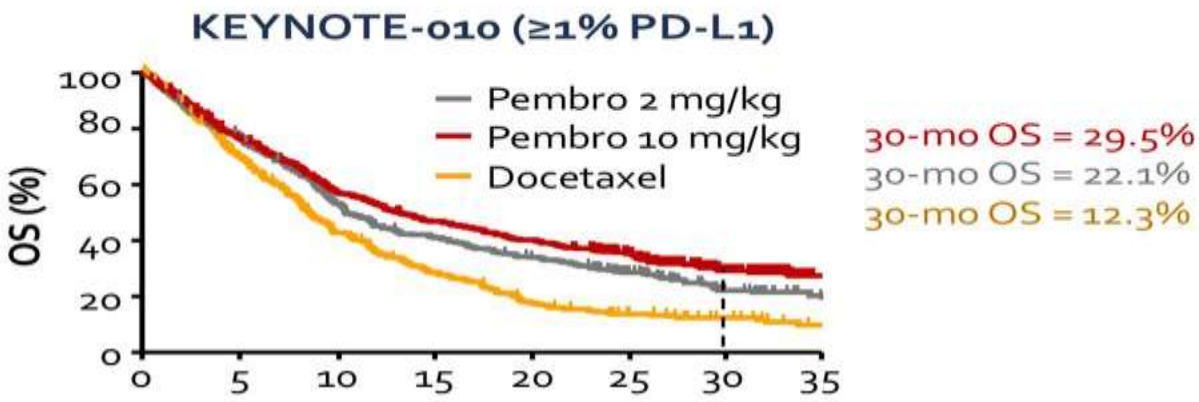
Overview of Immunotherapy as Second-line or Subsequent Therapy for Advanced NSCLC

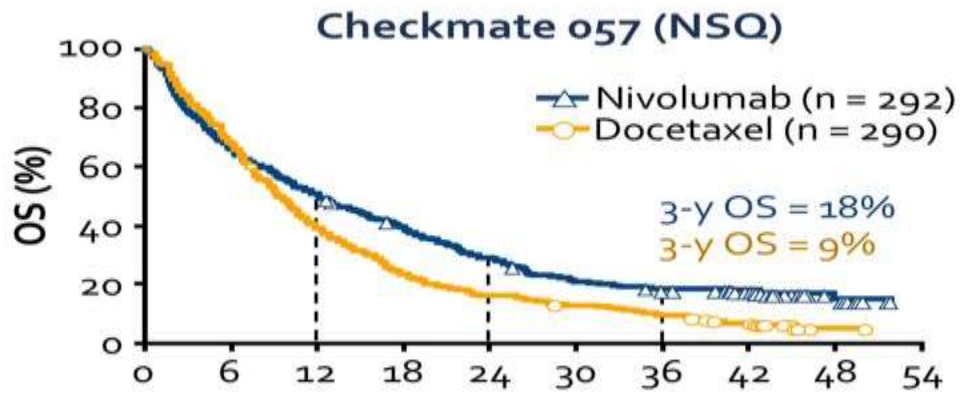
Compound	Trial	ORR, %	PFS, Mos (Range)	OS, Mos (Range)
Nivolumab	CheckMate 017[1]	20.0	3.5 (2.1-4.9)	9.2 (7.3-13.3)
	CheckMate 057[2]	19.2	2.3 (2.2-3.3)	12.2 (9.7-15.0)
Pembrolizumab	KEYNOTE 010*[3]	18	3.9 (3.1-4.1) 4.0 (2.7-4.3)	10.4 (9.4-11.9) 12.7 (10.0-17.3)
Atezolizumab	OAK[4]	14.0	2.8 (2.6-3.0)	13.8 (11.8-15.7)

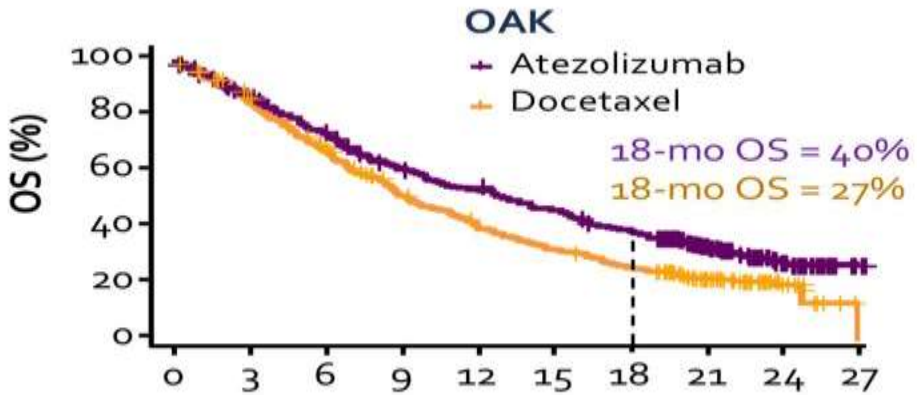
	Checkmate 017[1]		Checkmate 057[1]		KEYNOTE 010[2]			POPLAR[3]	
	Nivo (n=113)	**DTX** (n=129)	**Nivo** (n=287)	**DTX** (n=268)	**Pembro** 2 mg/kg (n=339)	**Pembro** 10 mg/kg (n=343)	**DTX** (n=309)	**Atezo** (n=142)	**DTX** (n=135)
TRAEs, % Any grade	61	87	71	88	63	66	81	67	88
Grade 3–4	8	56	11	54	13	16	35	12	39
Grade 5	0	2	<1	<1	1	1	2	1	2

A consistent but limited OS benefit in 2nd line



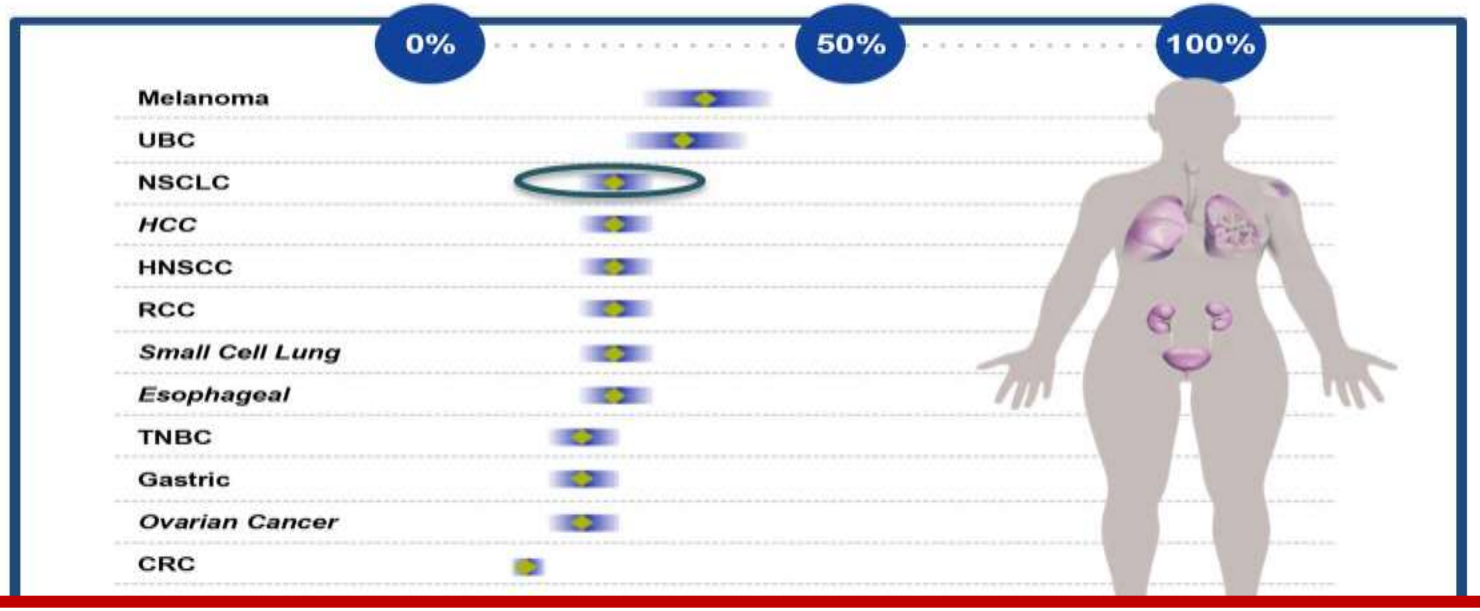






Felip, ESMO 2017; Herbst, ASCO 2017; Rittmeyer, Lancet 2017

Anti PD(L)-1 monotherapy results in response in a minority of cancer patients



Selection of Patients

1) Clinical Features

- Multivariate analyses showed no impact on survival for age, sex, TNM stage, or histology
  - Patients with brain metastases had poorer survival and response (RR: 16%)
  - Patients with ECOG PS ≥ 2 had poorer survival and response (RR: 12%)

Characteristics	Univariate Analysis			Multivariate Analysis (n = 889)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
ECOG PS ≥ 2 (vs 0/1)	2.24	1.85-2.72	< .0001	2.21	1.82-2.69	< .0001
Brain metastasis Yes (vs no)	1.39	1.15-1.68	.001	1.38	1.15-1.67	.0007

Molinier O, et al. WCLC 2017. Abstract OA 17.05. Girard N, et al. ESMO 2017. Abstract 1302PD.

2) Use of Steroids at Treatment Initiation

- 640 patients receiving single agent PD-1/PD-L1 inhibitor at MSKCC or Gustave Roussy
  - Identified 90 patients (14%) receiving ≥ 10-mg/day prednisone equivalents a the time of starting PD-1/PD-L1 therapy
    - Indications: dyspnea (33%), fatigue (21%), brain metastases (19%)
  - Baseline steroids associated with decreased ORR and shorter PFS and OS

Cohort	PFS		OS		ORR With Steroids, %	ORR, No Steroids, %
MSKCC	HR: 1.9	*P* < .01	HR: 2.7	*P* < .01	6	19
GRCC	HR: 1.6	*P* = .04	HR: 2.5	*P* < .01	8	18

Arbour KC, et al. ASCO 2018. Abstract 9003.

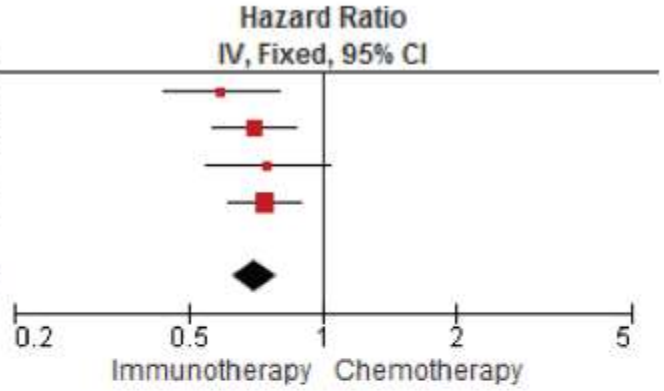
3) Smoking Status

In second-line setting, ICI therapy improved OS vs CT in ever-smokers but not in never-smokers

OS in Smokers

Study or Subgroup	log[Hazard Ratio]	SE	Immunotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CheckMate 017	-0.5279	0.1525	121	129	15.5%	0.59 [0.44, 0.80]
CheckMate 057	-0.3567	0.1094	231	227	30.2%	0.70 [0.56, 0.87]
POPLAR	-0.2877	0.1672	117	114	12.9%	0.75 [0.54, 1.04]
OAK	-0.3011	0.0935	341	353	41.3%	0.74 [0.62, 0.89]
Total (95% CI)			**810**	**823**	**100.0%**	**0.70 [0.63, 0.79]**

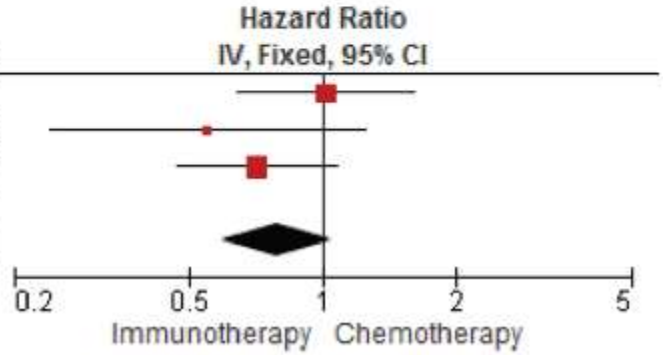
Heterogeneity: Chi² = 1.78, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 5.85 (P < 0.00001)



OS in Non-Smokers

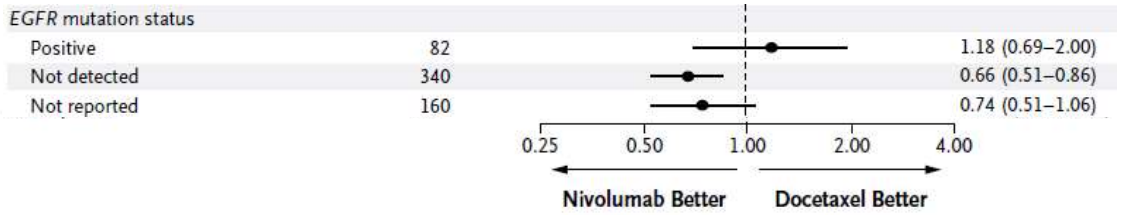
Study or Subgroup	log[Hazard Ratio]	SE	Immunotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CheckMate 057	0.0198	0.2353	58	60	39.3%	1.02 [0.64, 1.62]
POPLAR	-0.5978	0.421	27	29	12.3%	0.55 [0.24, 1.26]
OAK	-0.3425	0.2122	84	72	48.4%	0.71 [0.47, 1.08]
Total (95% CI)			**169**	**161**	**100.0%**	**0.79 [0.59, 1.06]**

Heterogeneity: Chi² = 2.17, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 1.57 (P = 0.12)

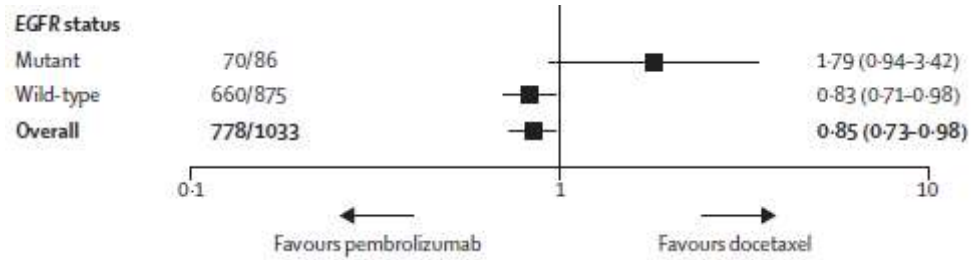


Kim JH, et al. Oncotarget. 2017;8:93149-93155.

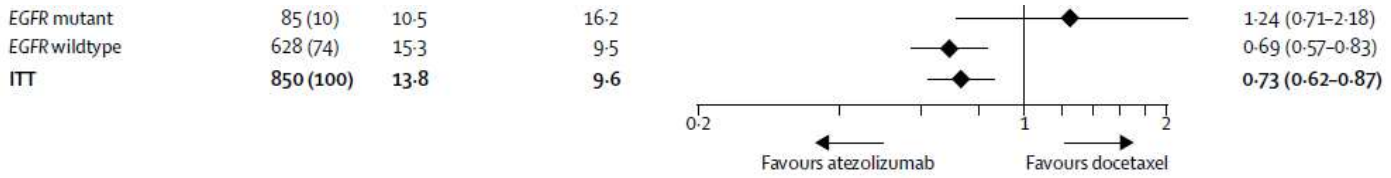
4) EGFR Mutation–Positive Adv NSCLC



CHECKMATE 057
Nivolumab vs Docetaxel



KEYNOTE-010
Pembrolizumab vs Docetaxel



OAK
Atezolizumab vs Docetaxel

- In retrospective analysis, 3.6% response to PD-L1 pathway inhibitors (n = 28) compared with 23.3% (n = 30) in similar *EGFR* WT cohorts[5]
  - Few patients with both PD-L1 ≥ 5% and high CD8+ TILs (2%, n = 48)
- Retrospective analysis of PD-L1 expression in EGFR-mutant NSCLC found 49% of patients PD-L1 negative and only 8% with PD-L1 ≥ 50%, and TMB largely low[6]
  - Comparison for all NSCLC: PDL1 0% (34%), PDL1 1-49% (38%), PDL1≥50% (28%)

1. Lee CK, et al. J Thoracic Oncol. 2017;12:403-407. 2. Lee CK, et al. JAMA Oncol. 2018;4:210-216. 3. Borghaei H, et al. N Engl J Med. 2015;373:1627-1639. 4. Herbst RS, et al. Lancet. 2016;387:1540-1550. 5. Gainor JF, et al. Clin Cancer Res. 2016;22:4585-4593. 6. Cho JH, et al. Cancer Res Treat. 2018;50:95-102.

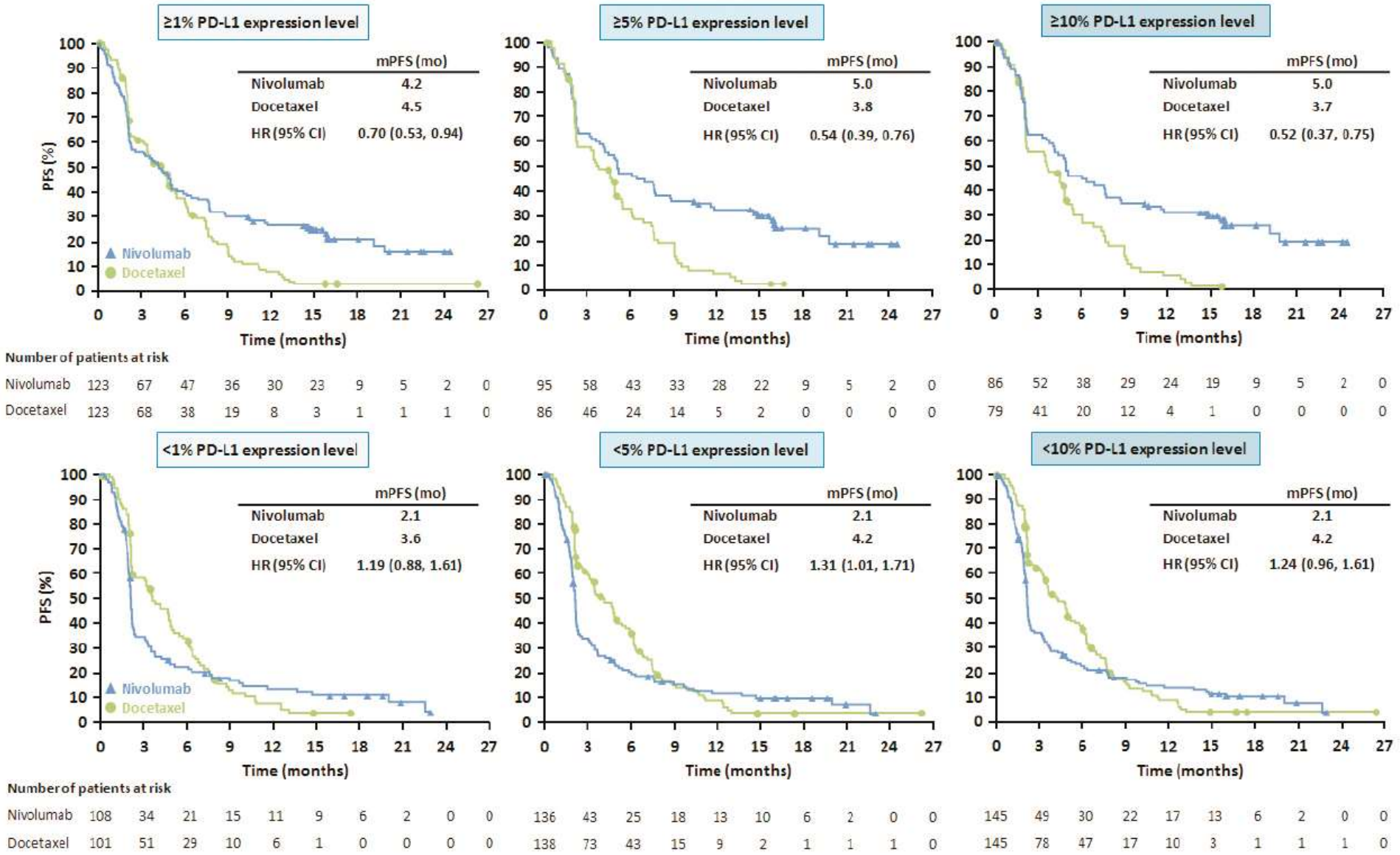
ImmunoTarget Cohort

Conclusion

Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	X	+	X	NA	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	X	X	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

5) Biomarkers: PD-L1 expression

Nivolumab



PD-L1 positivity
Present, absent, or graduated?

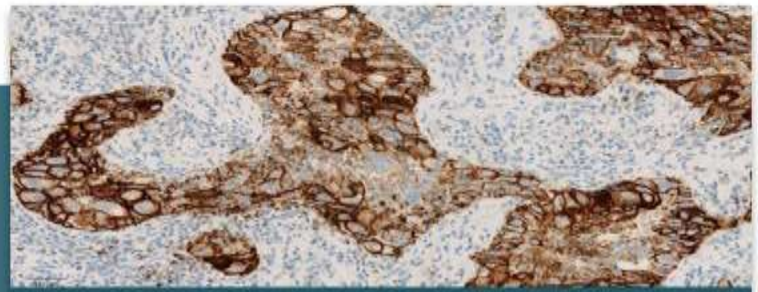
1%

Biomarker is ABSENT
or at a low level
You are unlikely to
benefit from therapy

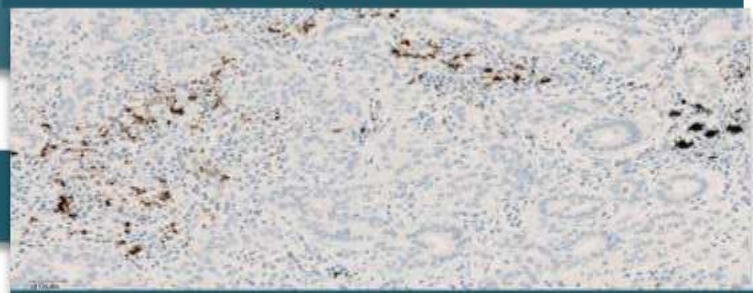
25%

50%

Biomarker is PRESENT
at an intermediate/high level
You are more likely to
benefit from therapy



Staining in tumor cells



Staining in immune cells

Biological continuum of biomarker expression

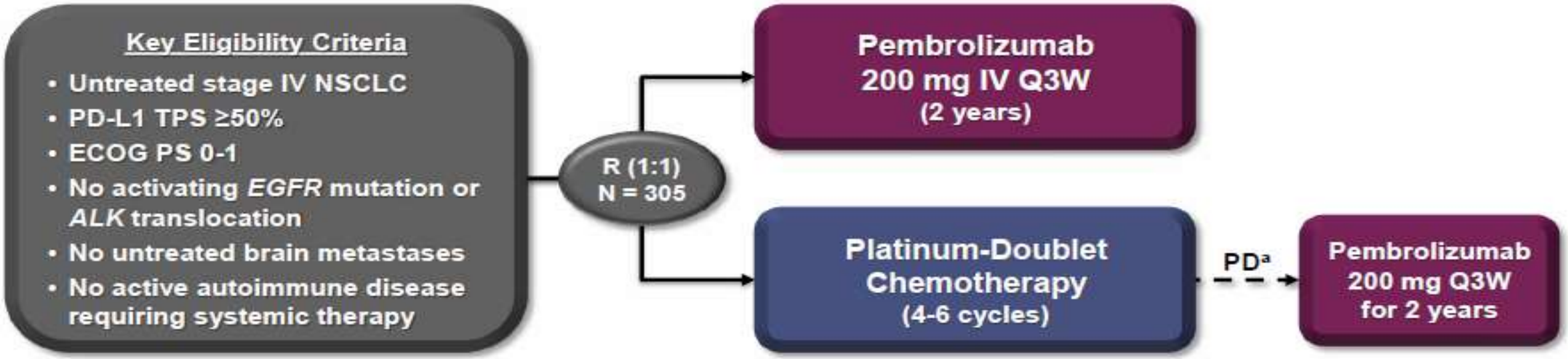
How do we define positivity?
Do we need cut-offs or intervals?
Where do we set the cutoff value?

KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced NSCLC With a PD-L1 TPS ≥50%

Martin Reck,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Melanie A. Leiby,[14] Gregory M. Lubiniecki,[14] Yue Shentu,[14] Reshma Rangwala,[14] and Julie R. Brahmer[15] on behalf of the KEYNOTE-024 investigators

[1]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; [9]Southern Medical Day Care Centre, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, London, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

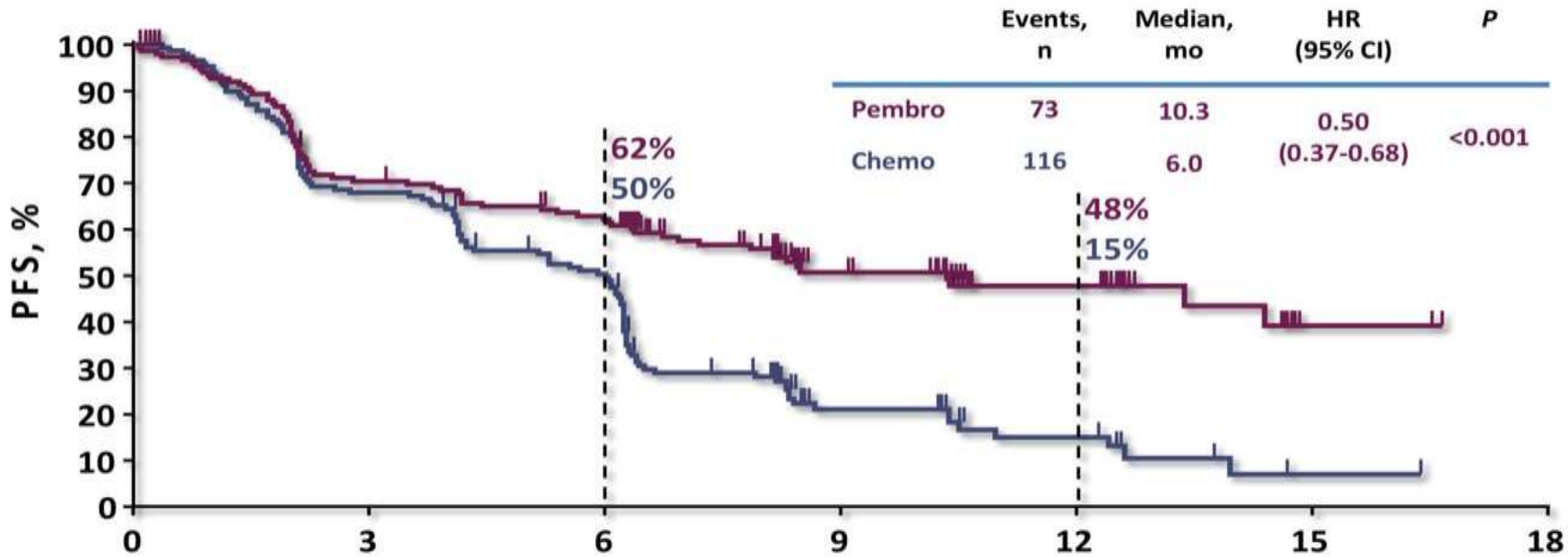
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

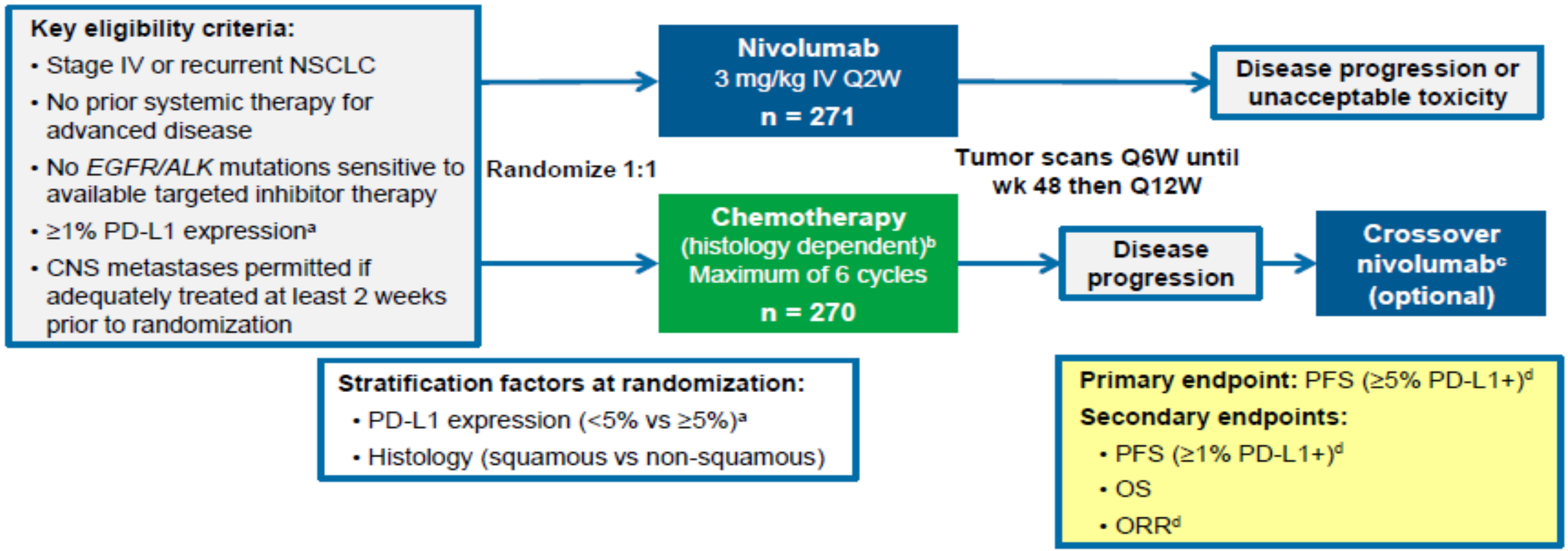
Pembrolizumab is better than chemo in PD-L1 ≥50% KEYNOTE-024



Primary endpoint PFS

Reck, NEJM 2016

Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



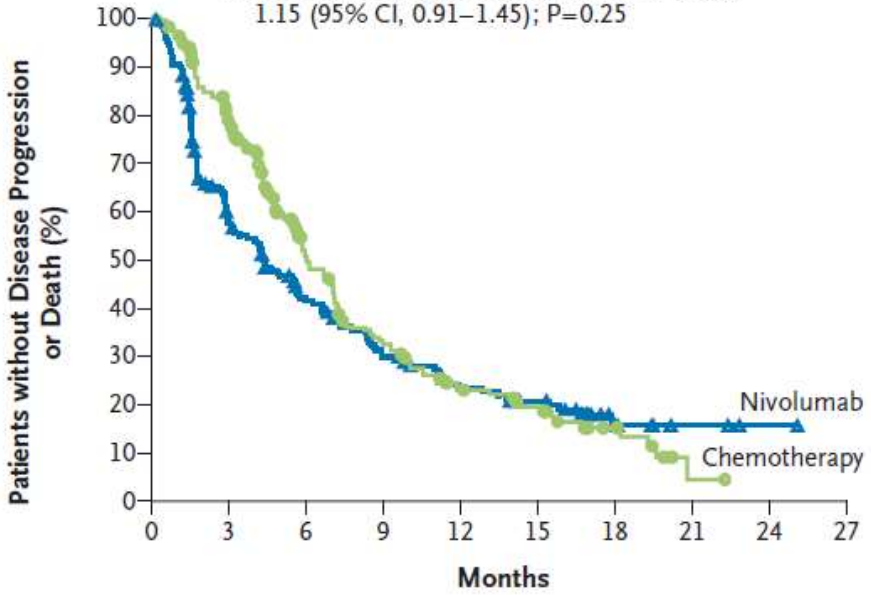
[a]Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized
[b]Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; Non-squamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy
[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review
[d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review

Nivolumab is not superior to chemotherapy in PD-L1 ≥5%

Progression-free Survival

	Median Progression-free Survival (95% CI)	1-Yr Progression-free Survival Rate
	mo	%
Nivolumab (N=211)	4.2 (3.0–5.6)	24
Chemotherapy (N=212)	5.9 (5.4–6.9)	23

Hazard ratio for disease progression or death, 1.15 (95% CI, 0.91–1.45); P=0.25



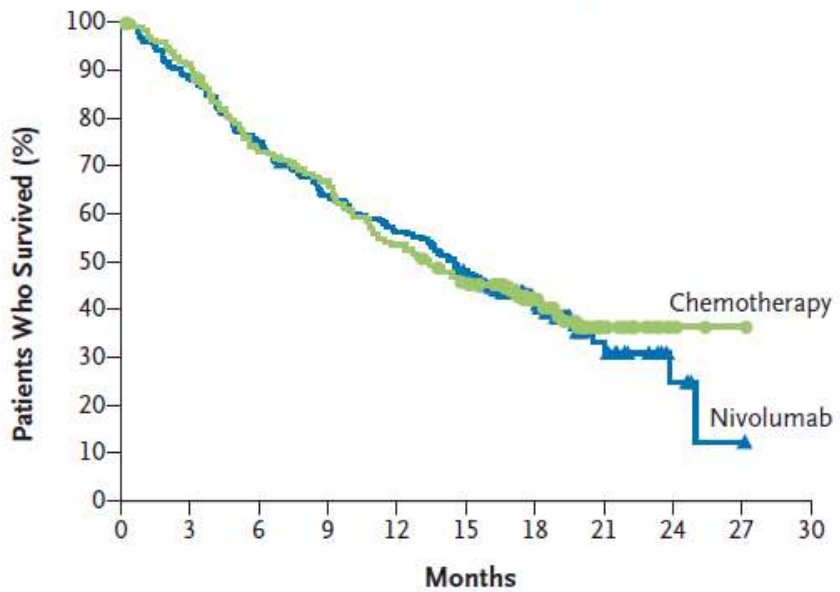
No. at Risk

Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

Overall Survival

	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate
	mo	%
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

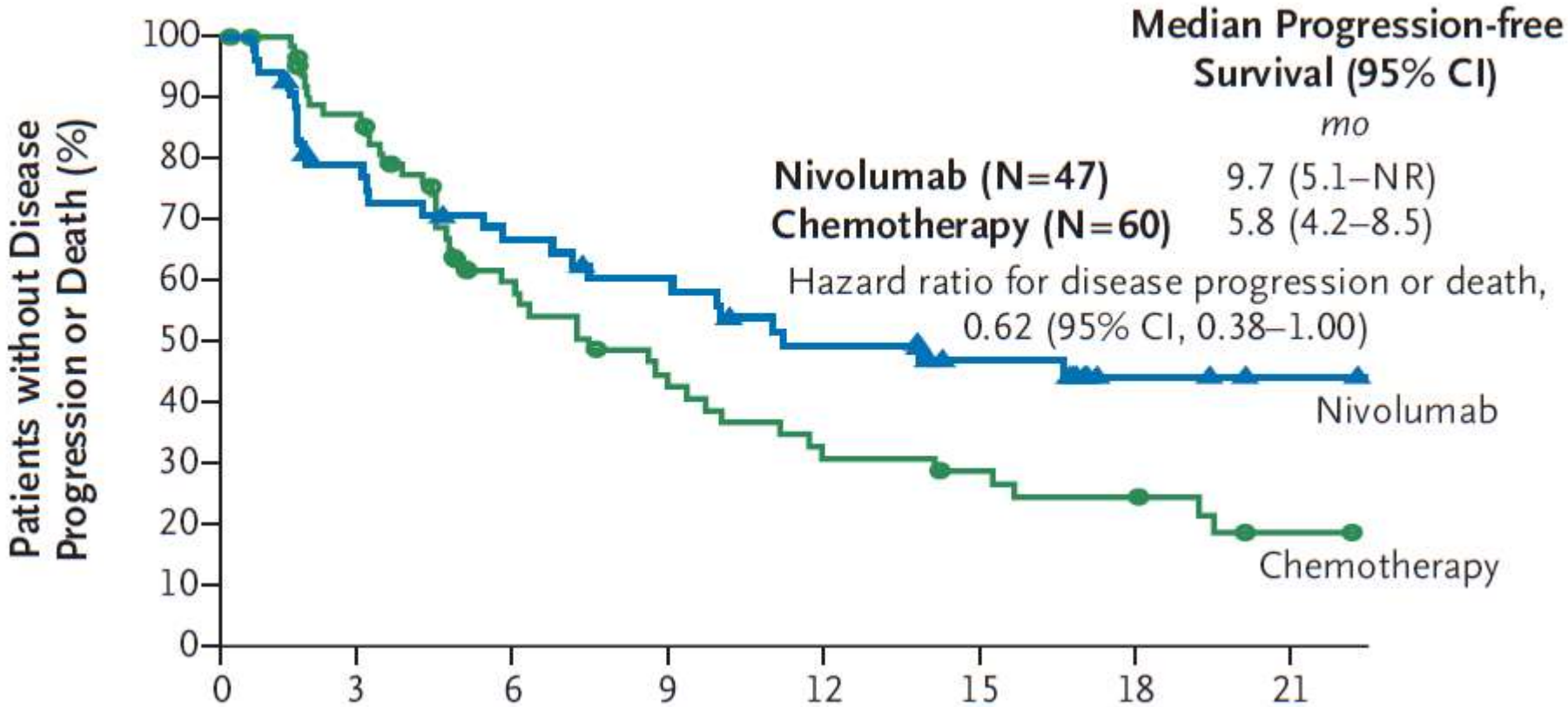
Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)



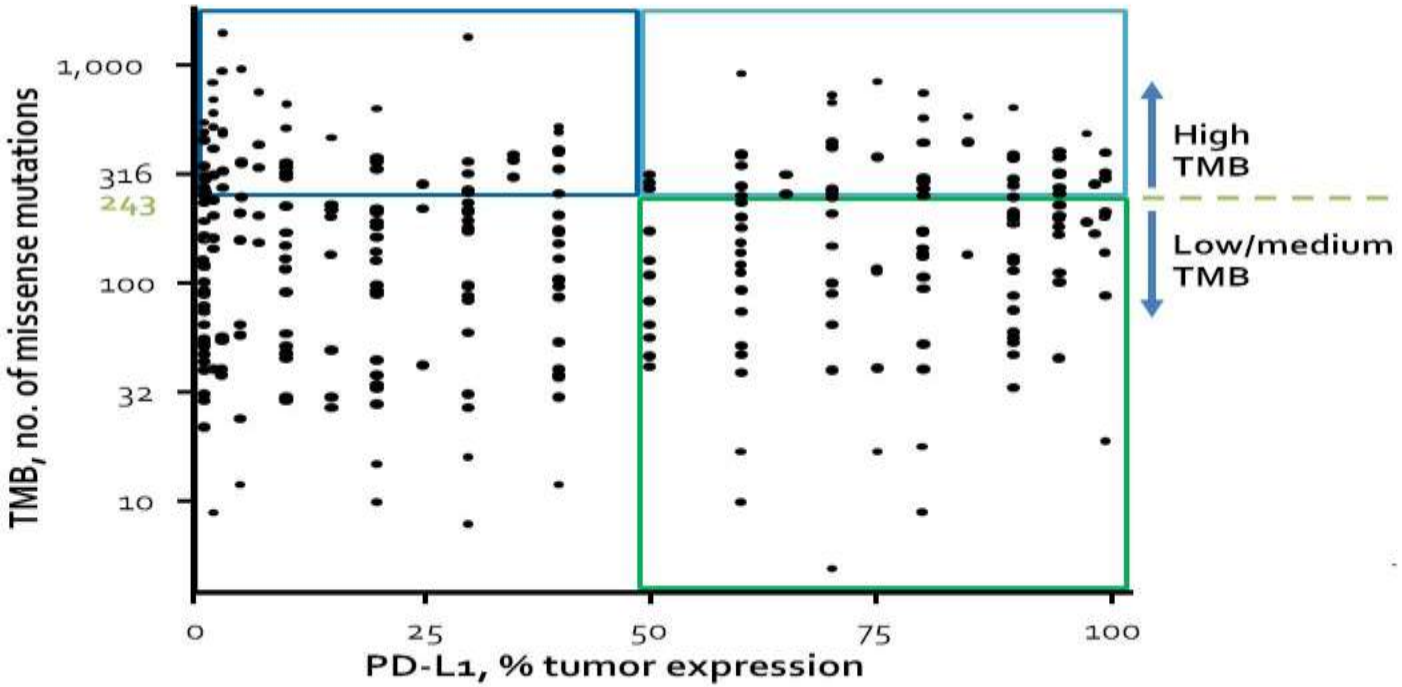
No. at Risk

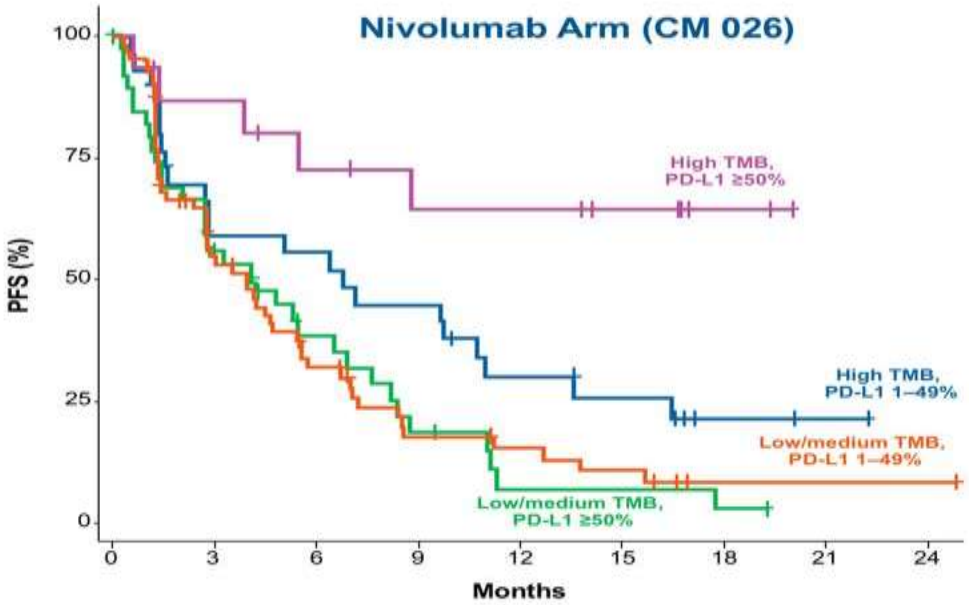
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

Progression-free Survival among Patients with High Tumor-Mutation Burden



TMB is not correlated to PD-L1 expression
Both biomarkers might be additive

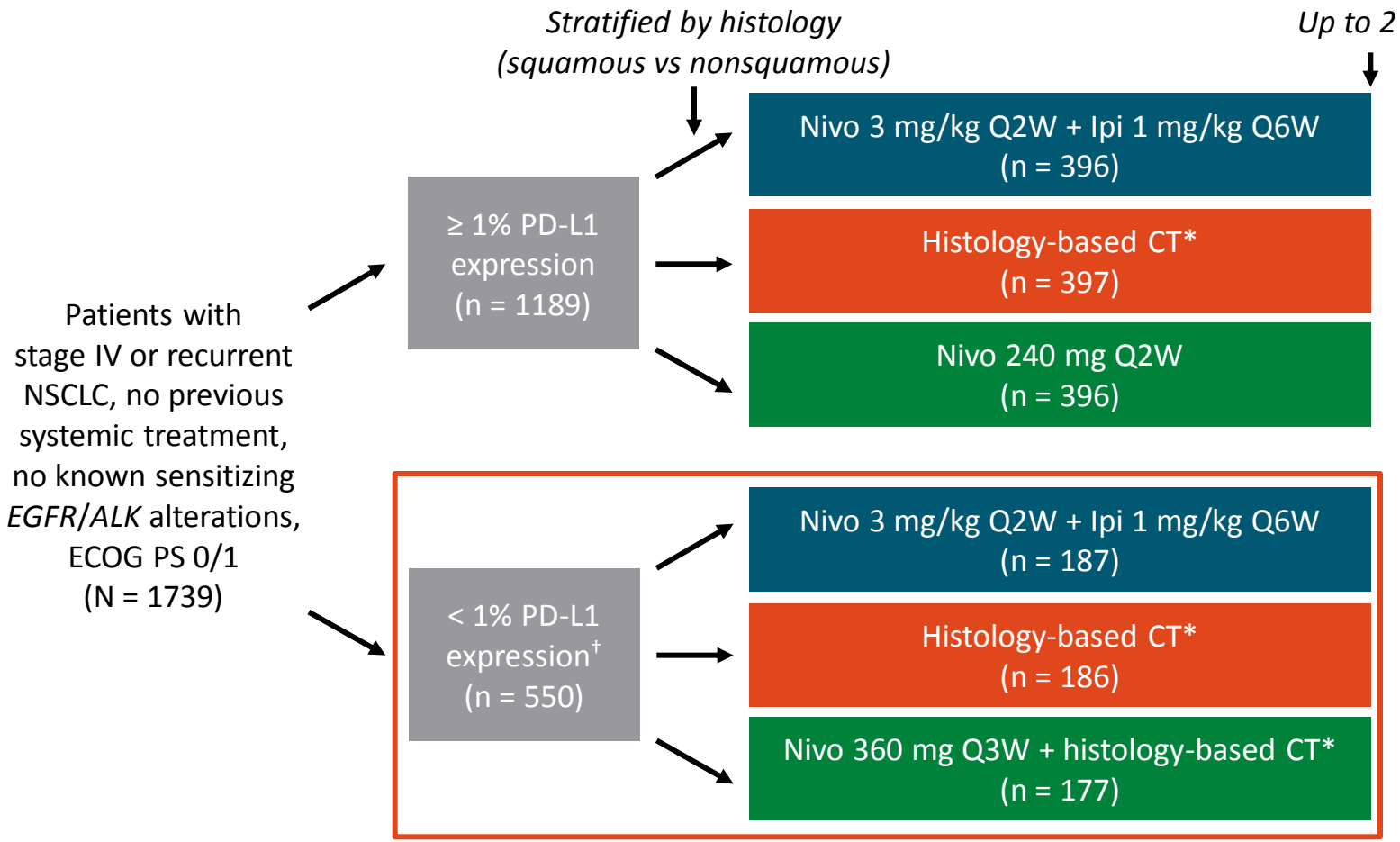




Peters, AACR 2017

CheckMate 227 Nivo+CT vs Nivo+Ipi vs CT in NSCLC : Study Design

- Randomized, open-label, multipart phase III trial



- Coprimary endpoints: OS in PD-L1–selected populations, PFS in TMB-selected populations receiving nivolumab + ipilimumab vs CT
- Secondary endpoint (current analysis): PFS in patients with < 1% PD-L1 expression receiving nivolumab + CT vs CT

*Nonsquamous: pem + cis or carbo Q3W for ≤ 4 cycles with optional maintenance (CT: pem; nivolumab + CT: nivolumab + pem); squamous: gem + cis or carbo Q3W for ≤ 4 cycles.
†1 patient randomized as < 1% PD-L1 and subsequently determined to have ≥ 1% PD-L1 expression.

Borghaei H, et al. ASCO 2018. Abstract 9001. ClinicalTrials.gov. NCT02477826.

CheckMate 227: Response in Patients With < 1% PD-L1 Expression

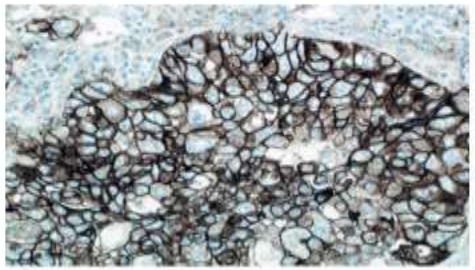
Response	Nivolumab + CT	Nivolumab + Ipilimumab	CT
Overall			
▪ ORR, n/N (%)	65/177 (36.7)	47/187 (25.1)	43/186 (23.1)
▪ Median DoR, mos	7.2	18.0	4.7
▪ ≥ 1-yr DoR, %	28	72	24
TMB ≥ 10 mut/Mb			
▪ ORR, n/N (%)	26/43 (60.5)*	14/38 (36.8)	10/48 (20.8)†
▪ Median DoR, mos	7.4	NR	4.4
▪ ≥ 1-yr DoR, %	33	93	NC

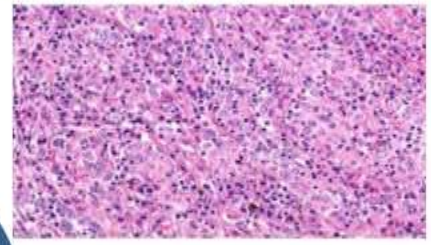
*For TMB < 10 mut/Mb, 27.8%. †For TMB < 10 mut/Mb, 22.0%.

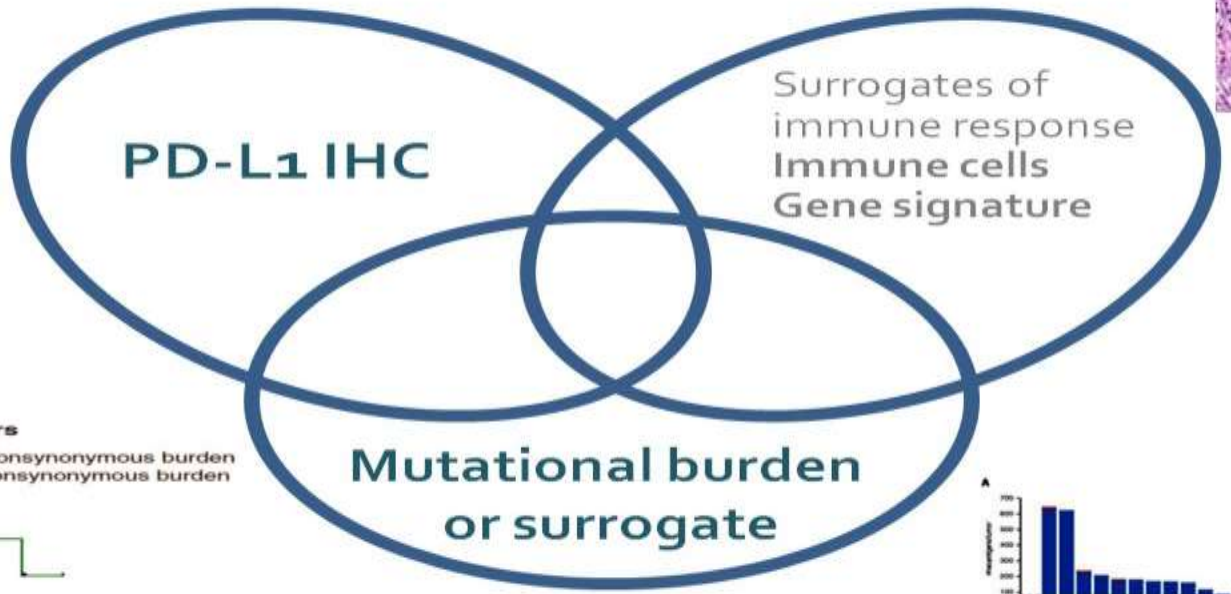
- Responses with nivolumab + ipilimumab appear to be very durable

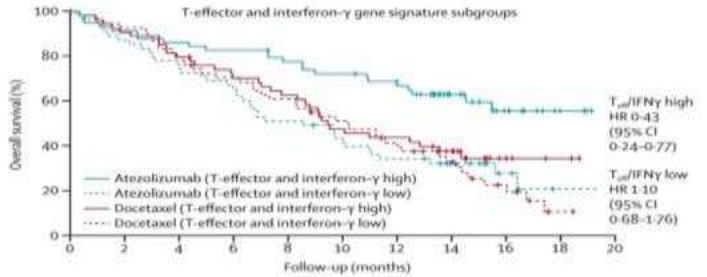
Borghaei H, et al. ASCO 2018. Abstract 9001.

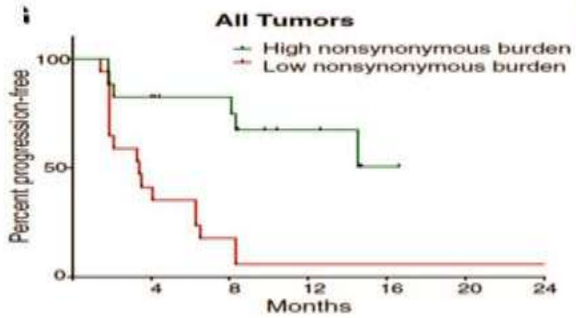
Biomarkers currently applied for NSCLC immunotherapy

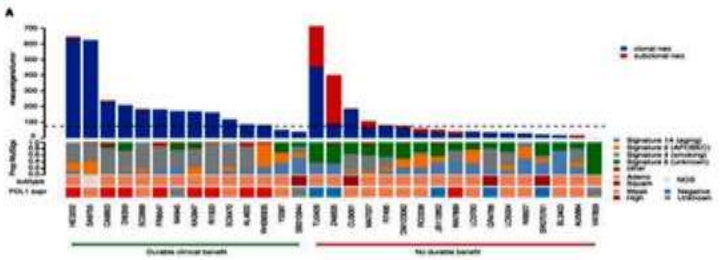






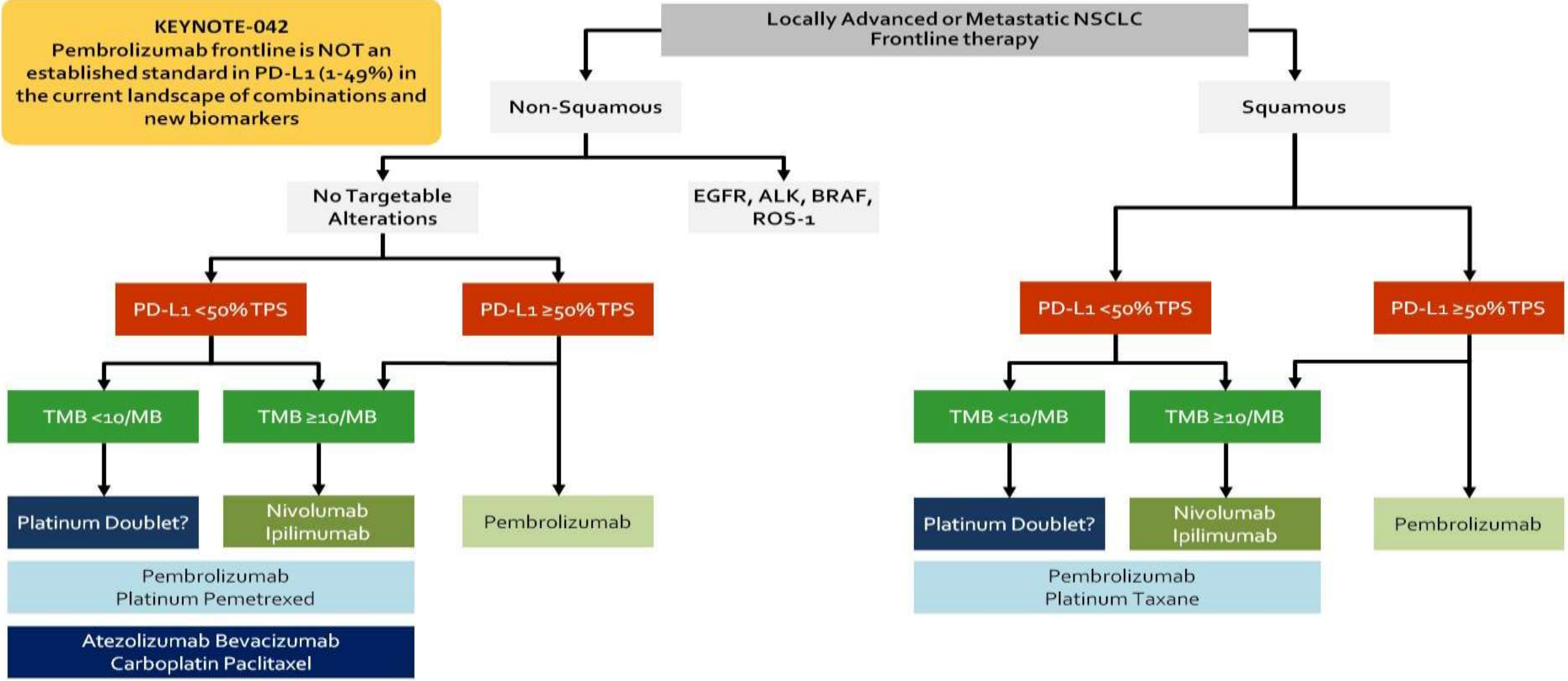






Rizvi, Science 2015; Fehrenbacher, Lancet 2016; McGranahan, Science 2016; Kerr, ASCO 2016

KEYNOTE-042
Pembrolizumab frontline is NOT an established standard in PD-L1 (1-49%) in the current landscape of combinations and new biomarkers



Peters S. ASCO 2018

Phase III KEYNOTE-189: First-line Platinum/Pemetrexed ± Pembrolizumab in Advanced NSCLC

Stratified by PD-L1 TPS (< 1% vs ≥ 1%), cisplatin vs carboplatin, smoking history (never vs former/current)

Patients with untreated stage IV nonsquamous NSCLC; *EGFR, ALK* neg; ECOG PS 0 or 1; any PD-L1 expression; no prior systemic treatment; no systematic brain metastases (N = 616)

2:1

Cisplatin 75 mg/m^2 or **Carboplatin AUC 5** + **Pemetrexed** 500 mg/m^2 + **Pembrolizumab** 200 mg Q3W for 4 cycles (n = 410)

Cisplatin 75 mg/m^2 or **Carboplatin AUC 5** + **Pemetrexed** 500 mg/m^2 + **Placebo** (normal saline) Q3W for 4 cycles (n = 206)

Maintenance

Pemetrexed 500 mg/m^2 Q3W + **Pembrolizumab** 200 mg Q3W for up to a total of 35 cycles

Pemetrexed 500 mg/m^2 + **Placebo** (normal saline) Q3W for up to a total of 35 cycles

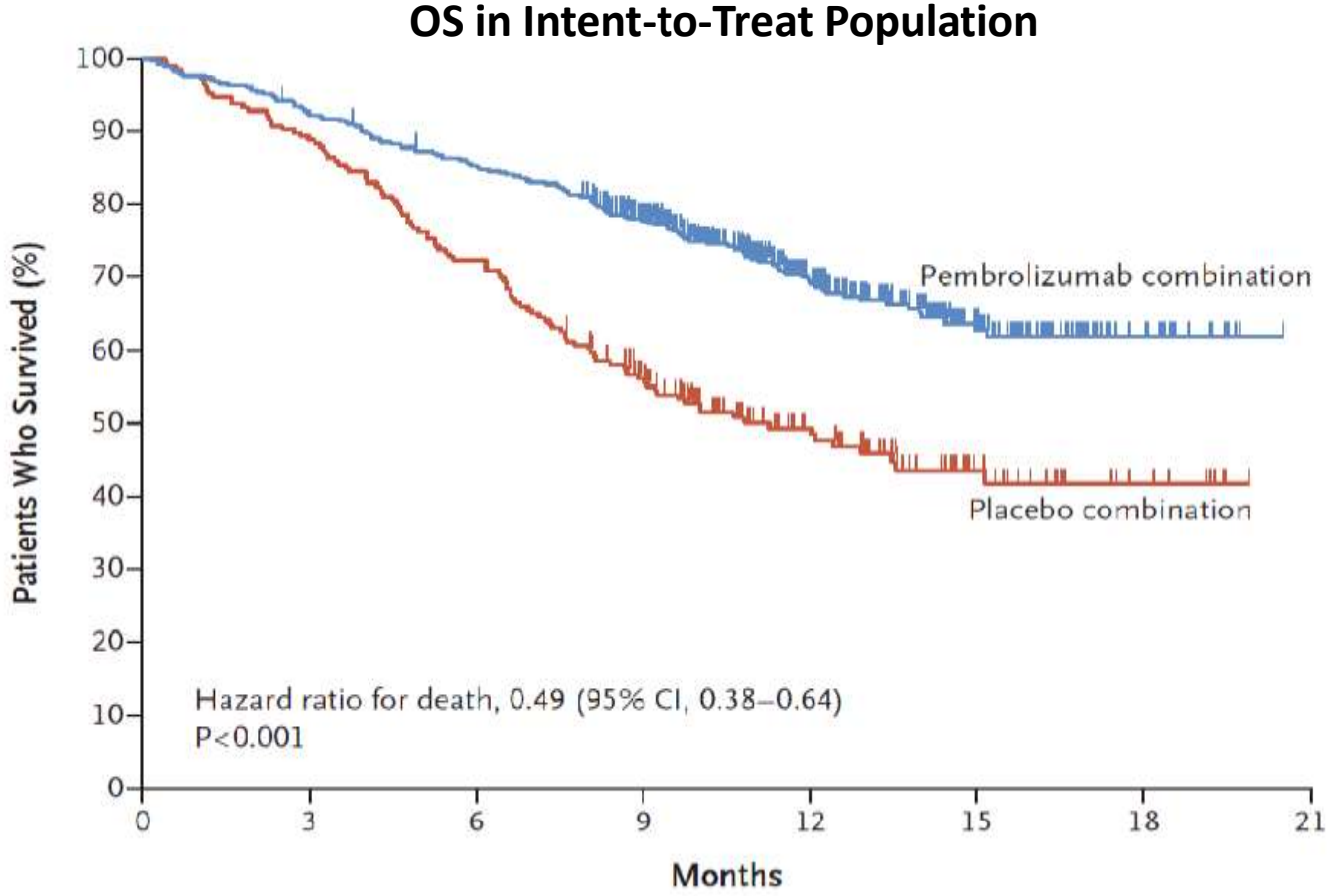
PD

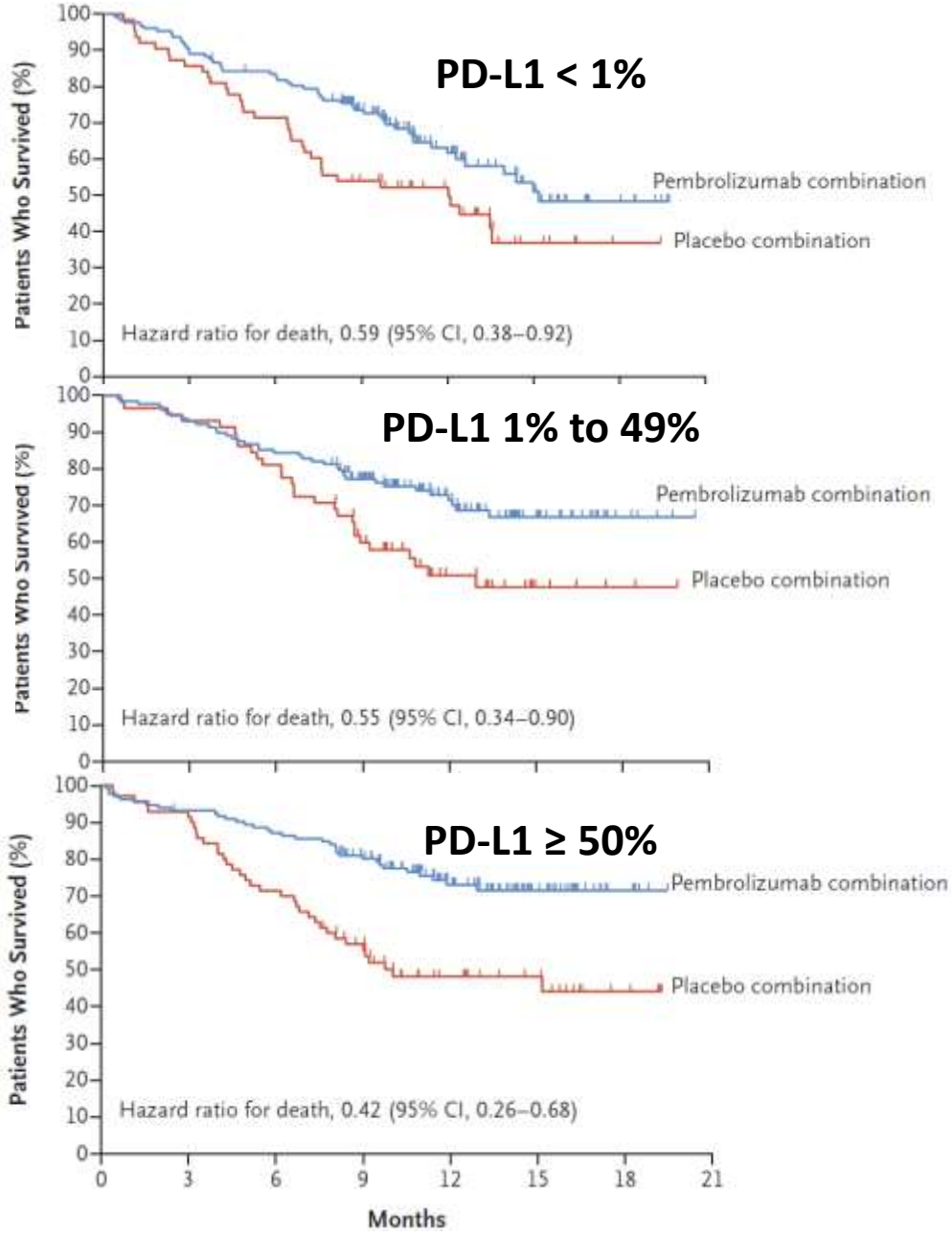
Pembrolizumab 200 mg Q3W for up to a total of 35 cycles

- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DoR, safety

Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

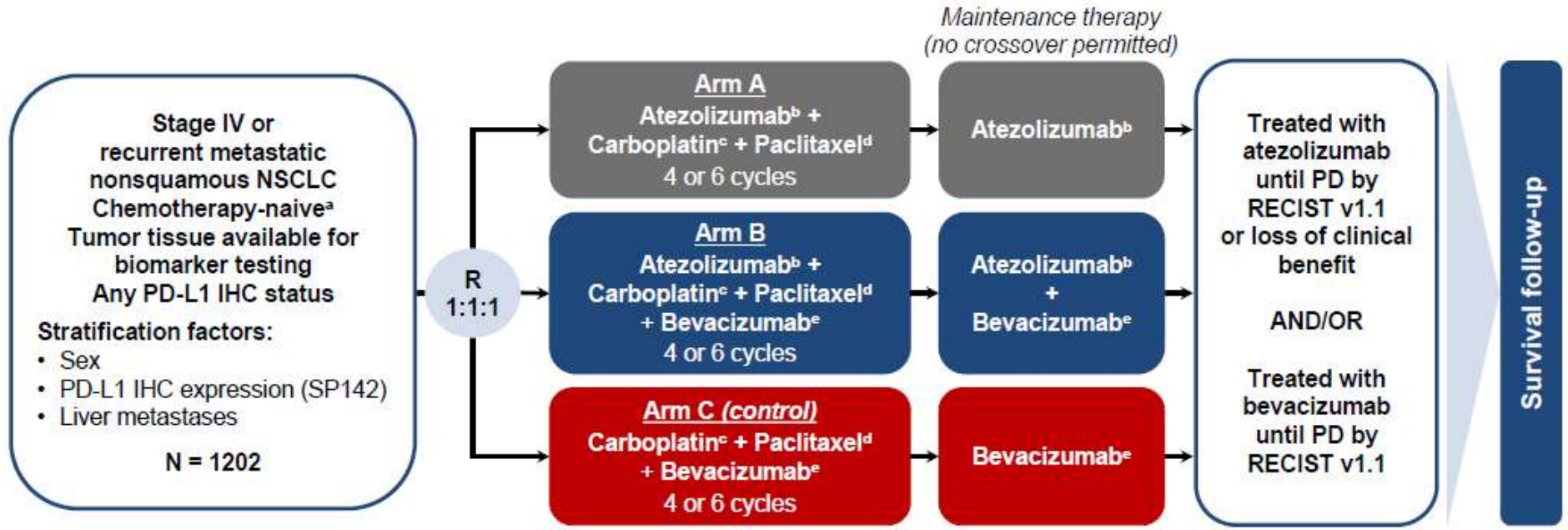
KEYNOTE-189: OS





Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print].

IMpower150: Atezolizumab + Carbo/Pac + Bevacizumab in Nonsquamous NSCLC



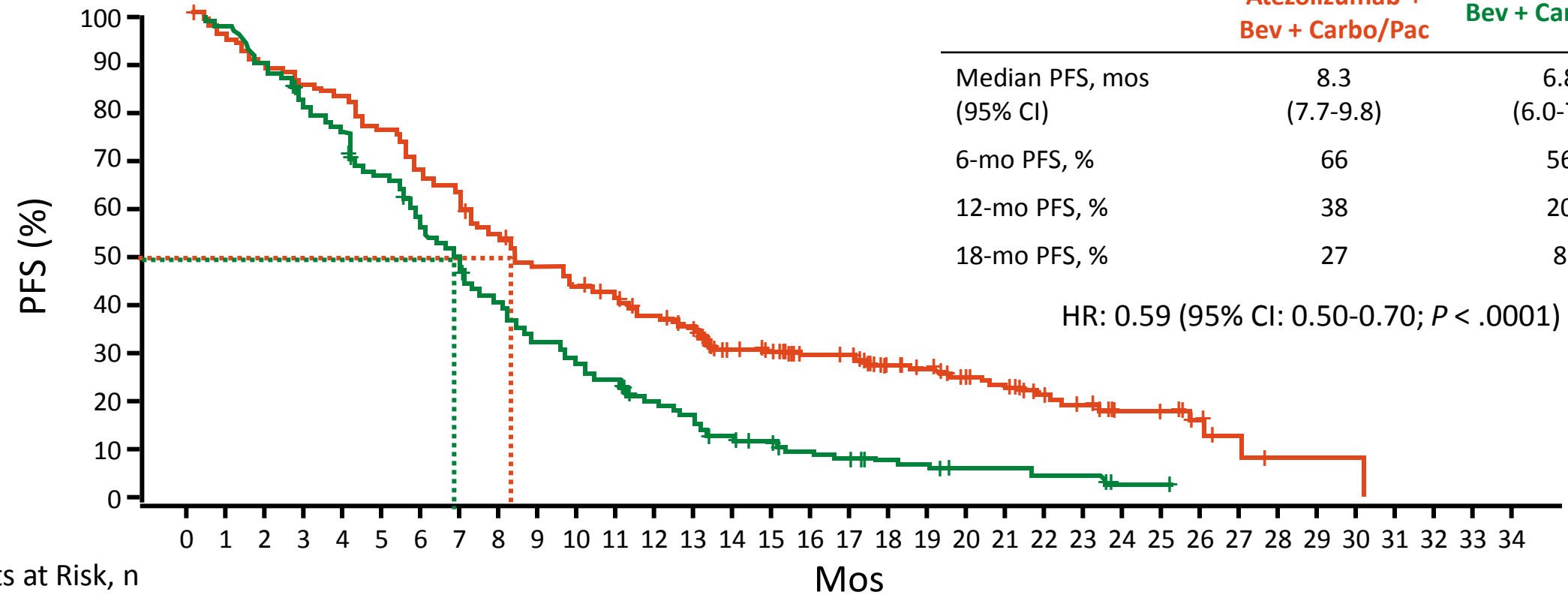
1 Co-primary objectives
- Investigator-assessed **PFS** in ITT-WT
- Investigator-assessed **PFS** in Teff-high WT
- **OS** in ITT-WT

2 Key secondary objectives
- Investigator-assessed **PFS** and **OS** in ITT
- Investigator-assessed **PFS** in PD-L1 IHC subgroups
- Independent review facility (IRF)-assessed **PFS**
- **ORR** and **DOR** per RECIST v1.1
- **Safety** in ITT

- Subgroup analysis of EGFR/ALK+ patients in Arms B and C (14% of ITT population) with progression or intolerance on targeted therapy prior to enrollment

Kowanetz M, et al. AACR 2018. Abstract CT076.

IMpower150: Updated PFS in ITT WT Population* (Coprimary Endpoint)



	Atezolizumab + Bev + Carbo/Pac	Bev + Carbo/Pac
Median PFS, mos (95% CI)	8.3 (7.7-9.8)	6.8 (6.0-7.1)
6-mo PFS, %	66	56
12-mo PFS, %	38	20
18-mo PFS, %	27	8

HR: 0.59 (95% CI: 0.50-0.70; *P* < .0001)

Patients at Risk, n

Atezolizumab + Bev + Carbo/Pac	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev + Carbo/Pac	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

*ITT WT: patients without *EGFR* or *ALK* genetic alterations; 87% of randomized patients.

Median follow-up: ~ 20 mos.

Socinski MA, et al. ASCO 2018. Abstract 9002. Reproduced with permission.

Conclusions

- Present:

  3 drugs approved with high activity in a limited population

- Future:

  Identify the right patient for right therapeutic schedule

  Increase the offer of theapeutic strategies in term of combination and schedule